1965

Birch reduction of benzamide, m-methoxy-benzamide and terephthalic acid

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BIRCH REDUCTION OF BENZAMIDE, m-METHOXYBENZAMIDE AND TEREPHTHALIC ACID

A Thesis

Presented to

the Faculty of the Graduate School

University of the Pacific

In Partial Fulfillment

of the Requirements for the Degree

Master of Science

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by

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May 1965

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Dated May 13, 1965

ACKNOWLEDGEMENTS

The writer wishes to express his sincerest thanks to his venerable teacher, Dr. Charles A. Matuszak, chairman of the thesis committee, who directed the research. Acknowledgement is also due to Dr. Emerson G. Cobb, chairman of the Chemistry Department for his considerations and criticism on the thesis. He is also indebted to Dr. Richard P. Dodge who commented on the thesis.

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INTRODUCTION

The reduction of aromatic rings with solutions of alkali or alkaline earth metals in liquid ammonia or amines, commonly known as Birch reduction, has become a useful means of producing certain alicyclic compounds (1,2,3). The usefulness of this reaction and its widespread application in syntheses has attracted increasing attention in recent years, primarily by Birch (2,3). The overall reaction is illustrated by the reduction of naphthalene in Figure 1, (5).

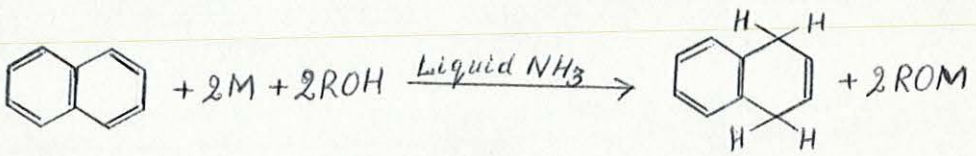


Figure I

In general, benzenoid compounds are reduced to the corresponding dihydro-derivatives, and Birch (1,7,36) has shown that further treatment of these products with solutions of metals in liquid ammonia and Proton Source can form tetrahydro-compounds. The last double bond is frequently left, since an isolated double bond reduces with more difficulty than conjugated ones.

The kinetic studies (8,11) of the metal-ammonia-

alcohol reduction of benzene has revealed that the reduction is of third order, being first order with respect to metal, to alcohol and to benzene. The rate equation governing these reductions may be expressed as:

$$-d(ArH)/dt = (ArH)(M)(ROH).$$

Where (ArH), (M) and (ROH) are the concentrations of aromatic hydrocarbon, metal and alcohol respectively. This expression was found to be valid for lithium reductions when the concentration of aromatic hydrocarbon is in the range 0.02-0.10 mole liter^{-1} and the concentrations of lithium and alcohol are in the range 0.04-0.20 mole liter^{-1}. Using the same technique (9,11,12) the relative rates of reduction with lithium, sodium and potassium were compared and found to decrease in that order. The reductions with lithium being much faster than with the other two metals.

Krapcho and Bothner-By pointed out that the validity of their kinetic analysis (8,11) depends on the assumptions that a single reaction path predominates and that no large concentrations of intermediates or of irreversible side reaction products occur (12). These assumptions very probably hold for the lithium reductions of benzene which are relatively rapid and which yield product in excess of 90%, but as pointed out by Eastman, Keenan and Secor (9,12), may not hold for the slower sodium and potassium reductions in which hydrogen evolution can compete appreciably with

reduction. This kinetic study is consistent with a radical-anion mechanism proposed by Birch (see Figure 4). Polycylic compounds, however, probably go via a dianion path as is indicated by the isolation of disodium dianion of naphthalene, anthracene, and phenanthrene in Birch reduction (6,10).

Most probably these reductions involves addition of two electrons to an aromatic nucleus, followed by protonation (2,3,14,15). A more detailed mechanism, however, has remained the subject of much speculation. A less accepted mechanism for Birch reduction has been proposed by Huckel, Graf and Munkner (17), in which the initial step is the addition of a hydrogen atom through a ternary collision of a benzene molecule, a proton donor and a solvated electron, Figure 2.

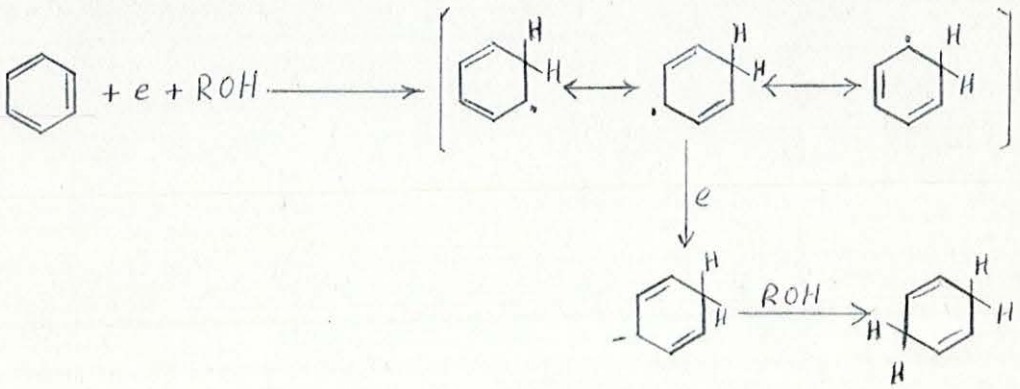


Figure 2

The observed kinetic data is also in agreement with this mechanism. But the evidence upon which this hydrogen-addition mechanism has been based, has been criticized as

being either incorrect or inapplicable (5,13).

The more accepted (5,13) anion mechanism is based on the equilibrium A involving the initial electron addition, Figure 3.

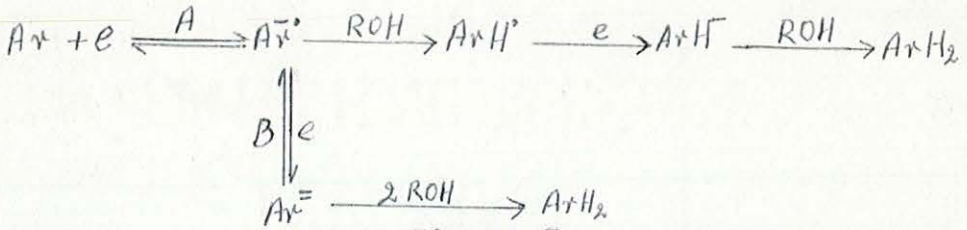
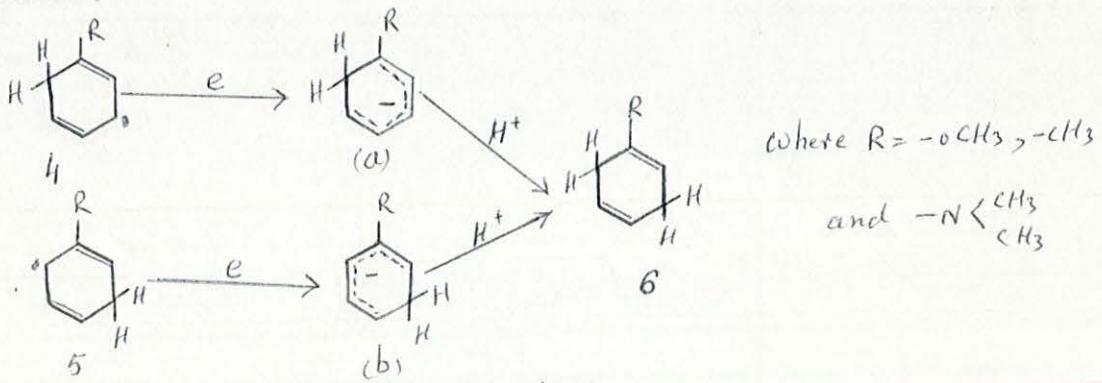


Figure 3

The equilibrium A will be expected to be on the left in monobenzenoid compounds because of the unfavorable resonance energy change involved in the formation of $A\bar{r}^{\cdot}$. The equilibrium B involving the addition of a second electron to form a dianion, probably does not occur except in polycyclic compounds. Reduction occurs only in the presence of a suitable proton source (5,13). Ammonia because of its low acidity (pKa 34) cannot provide the necessary proton but alcohols (pKa 16-18) can do so. Subsequent stages will then be rapid and probably irreversible.

The above radical anion mechanism can also be used to predict the nature of the principal reduction products of monobenzenoid compounds as follows (5,12). The structures of the dihydro-benzenes will be determined by a) the point of addition of the first proton to the radical-anion $A\bar{r}^{\cdot}$ and b) the point of addition of the second proton

to the mesomeric anion ArH^-. The expectation is that proton addition to $Ar^{\cdot}$ should occur in the position of greatest free charge density which according to Birch (5,12,13) is meta- to an ortho-, para- directing substituent, since according to Birch accumulation of charge in the ortho- and para- positions will be opposed by the substituent (5,37). However, according to Zimmerman (4), who calculated the charge distribution in the radical-anion intermediate for anisole, the greatest free charge density is ortho- (Figure 4), rather than meta- (Figure 5) to the methoxyl function. Addition of the second electron to the radical $ArH^{\cdot}$ (Figure 4 or 5) should give the corresponding mesomeric anion (a or b) as illustrated below with toluene, anisole and dimethylaniline:

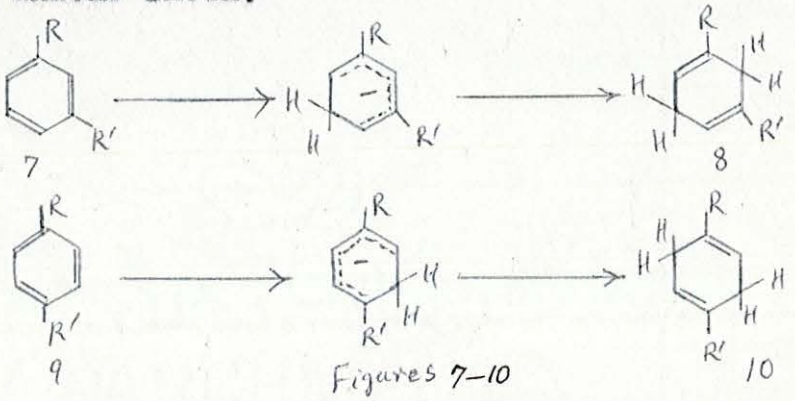


Figures 4-6

For irreversible proton addition, the products will be determined by relative rates of combination of the proton with the positions in the anion where free charge density can appear; that is the reaction will be kinetically controlled. The predominant product will then be that formed

by addition of proton at the position of greatest free-charge density which is in the middle of the mesomeric system (3, 37) and correspond to the 2- or 5- position (a or b) respectively. Thus forms the unconjugated isomer, Figure 6, rather than a thermodynamically more stable conjugated diene.

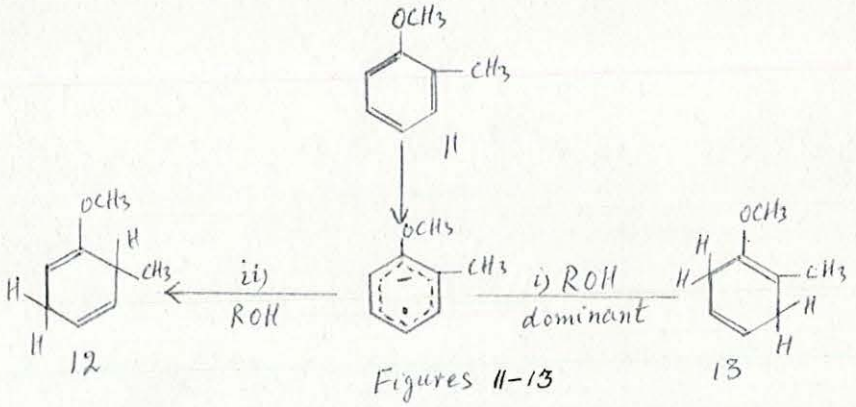
On the same basis when two or more substituents are present, addition would be expected: i, meta- to the most strongly ortho-, para- directing group; ii, preferably not in a position occupied by an ortho-, para- directing group. With meta- or para- dialkyl-, dimethoxy-, alkylmethoxy- etc. benzenes the results agree with the predictions; thus the disubstituted benzenes, Figure 7 and 9 (where R is more electron releasing than R) would be expected to proceed to the 2:5 dihydro-benzenes, Figure 8 and 10 through the intermediate anions shown:



Figures 7–10

Benzenes with ortho- substituents are more complicated, and give a mixture of two possible isomers. The predominent isomer is that formed by hydrogen addition to the unsubstituted position. Thus o- methylanisole gives a mixture

of the 2:5- and 3:6- dihydro-derivatives, Figure 12 and Figure 13, in which the latter predominates (19).



Figures 11-13

Substitution of a benzene nucleus with electron releasing groups (such as alkyl group and amino group; methoxyl group is an exception) in general decrease the ease of Birch reduction (5,12) and give 2,5- dihydroderivatives.

The substitution with electron withdrawing groups (such as carboxyl and amide groups) activate the benzene nucleus for reduction, and the added hydrogen atoms are directed to $\alpha\delta$- (or 1,4-) positions including the substituted positions. For these groups can stabilize the negative charges through resonance structures. Figure 14 (2,11,13).

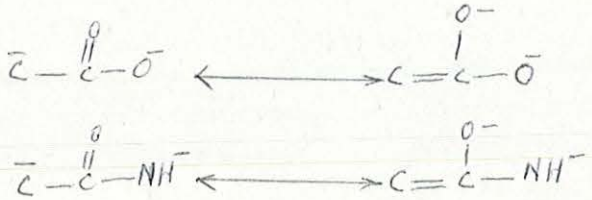
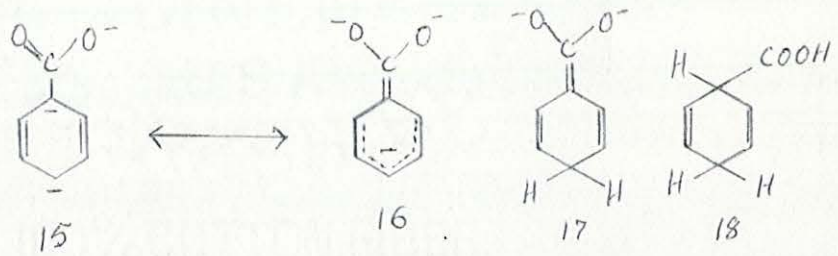


Figure 14

The proton addition might be expected to be para- to a meta-directing group, but in practice carboxyl is one group of this type which is not reduced before the ring (14). Thus in the reduction of benzoic acid, the dianion Figure 15 is believed to be formed before the protonation, since 1,4-dihydro-benzoic acid is formed even in the absence of alcohol (6). In the dianion Figure 15, the anionic charges are

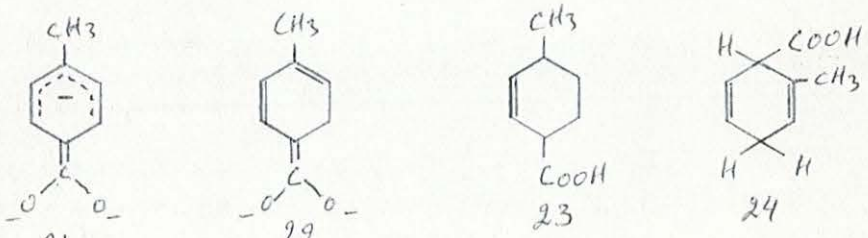


Figures 15-18

located para- to one another by their mutual repulsion and in the 1,4-positions by the stabilization of one charge by the carboxylate group, Figure 16. Protonation of the resulting anion at the carbon-position of greatest free charge density would then give the mesomeric anion Figure 17. The protonation of such anions by alcohols in liquid ammonia is known to be kinetically controlled giving the corresponding 1,4-dihydrobenzoic acid, Figure 18 (20,12). Similarly, o-toluic acid Figure 19, gives the 1,4-dihydro-acid, Figure 20, on reduction with sodium and alcohol in liquid ammonia. Under the same conditions, however, p-toluic acid

Figures 19-20

gives a tetrahydro acid (20). This result has been explained on the assumption that in the mesomeric anion, Figure 20, formed by the addition of two electrons to the p-toluate anion, the electron releasing methyl group reduces the negative charge density at the 4-position sufficiently to allow protonation at the 2- and 6-positions to become dominant. The product Figure 22, containing conjugated

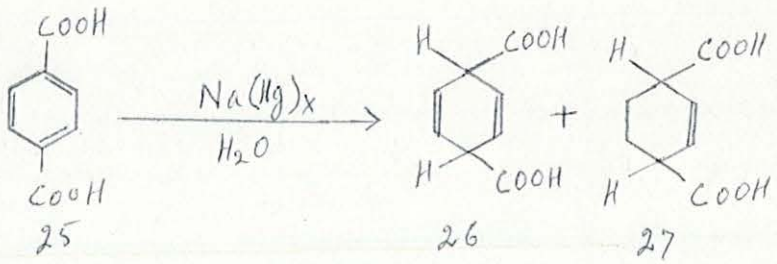


Figures 21-24

double bonds then would undergo further reduction (20). Similarly m-anisic acid gives mainly tetrahydro-acid. Ortho-anisic acid is reduced mainly to 1,4-dihydro-2-methoxybenzoic acid, Figure 24 (6).

Terephthalic acid, Figure 25, on chemical reduction with pure sodium amalgam in water at a pH of 10-12 by one report (21) gives a mixture of 1,4-dihydro-, Figure 26,

and 1,2,3,4-tetrahydro-terephthalic acid, Figure 27. By another report (23) gives a mixture of cis- and trans- 1,4-dihydro terephthalic acid. However, the similar Birch

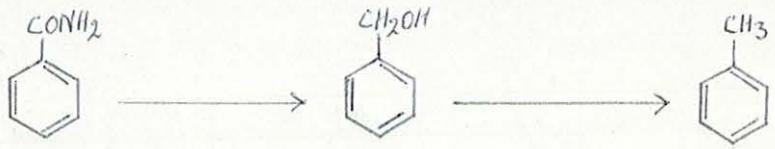


25 26 27

Figures 25-27

reduction of terephthalic acid with metal-alcohol in liquid ammonia has not been thoroughly examined. The products are not well defined (20) and have not been well examined.

Benzamide, Figure 28, is reported (20,24) to give benzyl alcohol and toluene, Figure 29, upon Birch reduction with sodium and ethanol in liquid ammonia. Thus instead of

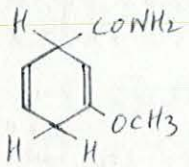


28 29

Figures 28-29

reduction of the aromatic ring, reduction of the amide group apparently occurred. Carboxylic amides are neutral substances but in liquid ammonia their acidic character is revealed by their electrical conductivity and ability to react with the more electro-positive metals with the formation of salts and the evolution of hydrogen (37,38).

However amides are less acidic than carboxylic acids. Substituents that would help to stabilize the amide anion could make the amide sufficiently acidic to form its anion in which form it is considered to be immune to reduction (20). Thus m-methoxybenzamide is reported (20) to be reduced to 1,4-dihydro-3-methoxybenzamide, Figure 30, when subjected to an excess of sodium in ammonia and ethanol. An excess of sodium must be used to satisfy the side reaction of sodium and ethanol, which occurs at a comparable rate. Similarly 3,5-dimethoxybenzamide is reported (20) to be reduced to 1,4-dihydro-3,5-dimethoxybenzamide, Figure 31.



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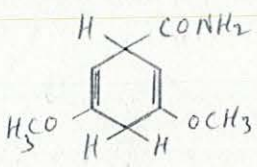
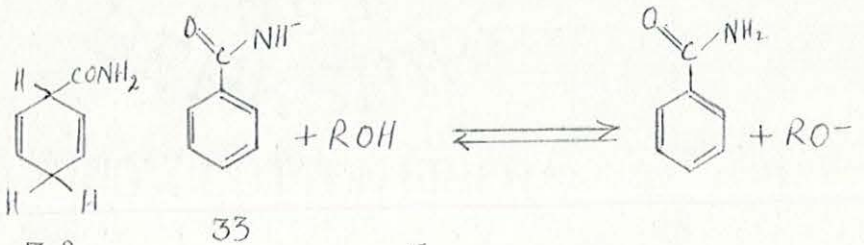


31

Figures 30-31

Although reduction of amide group of benzamide is reported, using sodium and ethanol (20), reduction of the ring to 1,4-dihydrobenzamide, Figure 32, was achieved in high yield by using t-butyl alcohol in place of ethanol (20). By using this less acidic proton source, stabilization of the amide as its anion, Figure 33, was rationalized as being possible and the rate of the competing reduction of amide group itself was slowed (20).



32 33

Figures 32-33

Recently, the reduction of the ring of benzamide with lithium in liquid ammonia and ethanol was reported by Niem (27) to yield 1,4-dihydrobenzamide in about 59% yield. By using lithium and adding ethanol slowly after the addition of the metal, the reduction of the ring was achieved.

Since the reported reduction of the ring of benzamide by the procedure using lithium and ethanol (27) is in contradiction with the results reported using sodium and ethanol (20), a more thorough examination of the reduction of benzamide is desirable. Similarly, the Birch reduction products of terephthalic acid need to be examined and characterized.

This thesis is a report of the examination of the Birch reduction of benzamide, m-methoxybenzamide and terephthalic acid.

RESULTS AND DISCUSSION

For the reduction of benzene and alkylbenzenes with alkali metals and alcohol in liquid ammonia solutions, it seems probable that the sequence of events is as represented in steps 1 through 5, Figure 34. (8). In this scheme, solvation by ammonia is represented by the symbol (s); the degree of solvation will vary from one species to the next.

Step 1. $M + s \rightleftharpoons M^{+}_{(s)} \cdots e^{-}_{(s)}$

Step 2. $M^{+}_{(s)} \cdots e^{-}_{(s)} + \bigcirc \rightleftharpoons M^{+}_{(s)} \cdots \bigcirc^{-}_{(s)}$ (I)

Step 3. $M^{+}_{(s)} \cdots \bigcirc_{(s)} + ROH \longrightarrow \bigcirc_{(s)} + ROM_{(s)}$

Step 4. $\bigcirc_{(s)} + M^{+}_{(s)} \cdots e^{-}_{(s)} \longrightarrow M^{+}_{(s)} \cdots \bigcirc^{-}_{(s)}$

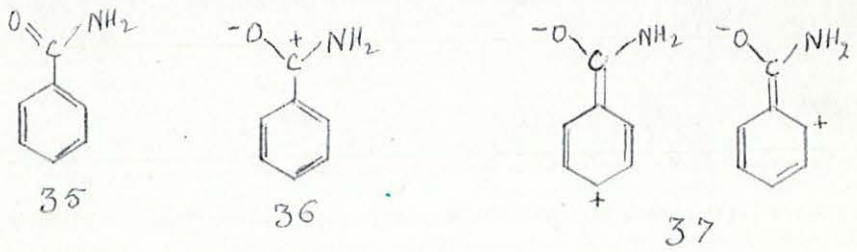
Step 5. $M^{+}_{(s)} \cdots \bigcirc^{-}_{(s)} + ROH \longrightarrow \bigcirc + ROM_{(s)}$

Figure 34

In step 1, the dissolved metal dissociates to form solvated electrons. Nuclear magnetic resonance of such solutions have indicated (28) that in concentrated solutions the electrons are in weakly bound states with the solvated cation, analogus to expanded s-orbitals. In dilute solutions more complete dissociation may occur. In step 2, a reversible equilibrium is set up, in which the electron is transferred to the aromatic ring, and the ion-pair I now consists of the solvated metal ion and the solvated anion-

radical. In step 3, the rate determining step, the anion radical reacts with a molecule of alcohol to release metal alkoxide, and form a radical intermediate. In rapid subsequent steps this intermediate acquires an additional electron, and abstracts a proton from alcohol to yield the 1,4- or 1,2- dihydro-derivative.

Generally hydrogens are added in positions (1,4) to each other, avoiding carbon atoms carrying electron repelling groups in the order $-N(CH_3)_2$, OMe alkyl, and being attracted to carboxyl or electron attracting groups (3). In benzamide, Figure 35, the deactivating effect of the amide group in electrophilic substitution reaction is attributed to electron attractive effects which may result from inductive, Figure 36, and mesomeric, Figure 37, factors. Mesomeric consideration indicates that the ortho- and para-positions are more electron deficient than meta-position.



Figures 35-37

The electron withdrawing effect of benzamide group would be expected to activate the benzene ring for Birch reduction, since a nucleophilic type addition of an electron to the

ring is involved. In terms of radical-anion mechanism Figure 4, the expectation would be that the addition of the first proton to anion-radical should occur in the position of greatest free charge density in the ring i.e., ortho- or para- to the amide group (27). Thus with benzamide, addition of second electron to the radical ArH* should give the mesomeric anion, Figure 38. The protonation of such anions in liquid ammonia is kinetically controlled (19) since the

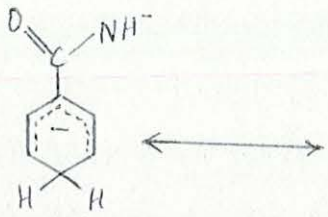


Figure 38

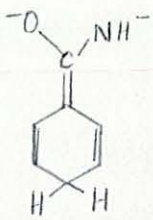


Figure 39

less stable, nonconjugated diene system is produced. So addition should occur at point of greatest free charge density which is located in the middle of mesomeric system (3,20,27), stabilized by the amide group and corresponds to 1-position in Figure 38. Thus 1,4-dihydro isomer results.

In terms of dianion mechanism, Figure 3, the anionic charges would be expected to be located para- to one another by their mutual repulsion and in the 1,4-positions by the stabilization of one charge by the amide group (8,20). Protonation of the resulting anion, Figure 40 at carbon position of greatest free charge density should give the mesomeric anion, Figure 41. The protonation of this anion

is kinetically controlled (20,27), and will give the 1,4-dihydrobenzamide, Figure 39.

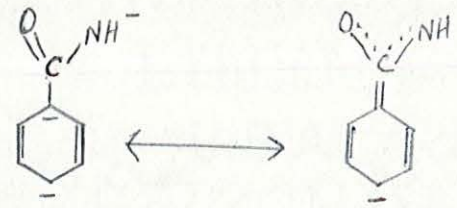


Figure 40

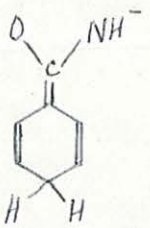


Figure 41

A comparison of acidity of benzamide with that of benzoic acid and m-methoxybenzoic acid, etc. is given in the following table.

TABLE I

PKa values (20,29)

	PKa
Benzoic acid	4.2
m-methoxybenzoic acid	4.09
Terephthalic acid	3.82
Benzamide	15-16
Ethanol	18

Thus the order of acidity is as follows:

$$\phi(COOH)_2 > \phi\langle^{COOH}_{OCH_3} > \phi COOH > \phi CONH_2$$

Since terephthalic acid, m-methoxybenzoic acid and benzoic acid are highly acidic, the carboxylic acid groups are in the anion form and are protected during Birch reduction (20). It has been reported (20) that the amide group of benzamide is reduced by Birch reduction when ethanol and sodium are used. It was proposed that since benzamide is weakly acidic, it is not in the anion form and the amide group is not protected. Recently Niem reported (27) that contrary to the previously reported results (20) benzamide is reduced to 1,4-dihydrobenzamide with lithium and ethanol. Again this may be attributed to either greater reduction potential of lithium (see Table II) or the use of a different procedure, first reported by Wilds and Nelson in 1953 (25,26), where lithium was added first and then the ethanol. They showed that it is advantageous to add the proton source (ethanol) to a mixture of the aromatic compound, lithium and ammonia, rather than adding the alkali metal last as had been done by Birch. The superiority of this procedure was proved later by Dryden, et al., (18).

The apparent superiority of lithium over sodium or potassium was attributed largely to its greater reduction potential as is seen from the following Table II (18).

TABLE II

Reduction Potentials of Alkali Metals in Liquid Ammonia

Metal	Reduction Potential
Lithium	-2.99
Sodium	-2.73
Potassium	-2.59

However, it has been reported (18) that the presence of small amounts (up to 1.5 ppm) of iron or copper does not have any appreciable effect on lithium reductions. On the other hand, with iron concentration of more than 1.0 ppm (commonly found in liquid ammonia), neithersodium nor potassium are useful reducing agents (18). Iron and copper catalyzes the side reaction between metal and alcohol.

In 1955, Birch and co-workers (29) showed that reduction of n-alkylamides with sodium-ethanol in liquid ammonia yields first benzaldehyde and then further reduction of this gives 1,4-dihydro-benzaldehyde. So in order to clarify Niem's and previous results (20,29) re-investigation of reduction of benzamide was necessary.

In the present investigation it was found that the reduction of ring instead of amide group of benzamide by Niem's procedure (27) was achieved and hence Niem's con-

clusion is confirmed (see Table III). It was also found in the present investigation that reduction of ring rather than amide group of benzamide took place in liquid ammonia with sodium and ethanol, see Experiments III and IV in Table III, by the Kuehne and Lambert's procedure (20) and dry-ice temperature (-65 to -78° C). However, when the reduction (Experiment V) of benzamide with sodium and ethanol by Kuehne and Lambert's procedure was carried out at boiling point of ammonia, -33° C, another product, m.p. 149-52° was obtained, which showed only end absorption in ultra-violet region (200-320 mm). The infrared spectrum was different than that of either pure benzamide or 1,4-dihydrobenzamide. It seems likely this new compound might be a tetrahydro-derivative. If so, various possibilities from the literature are:

a. 1-Cyclohexene-1-carboxamide, m.p. 126-8°C (30,33)

b. 2-Cyclohexene-1-carboxamide, m.p. 139-40°C (31)

c. 3-Cyclohexene-1-carboxamide, m.p. 152°C (32)

d. 3,5-Cyclohexadienamide, m.p. 121-3°C (34)

e. Hexahydro-benzamide, m.p. 184-85°C (35)

On the basis of U.V. absorption (a) and (d) can be eliminated, since the conjugated double bond system would absorb fairly strongly in the ultra-violet region. From the melting points, it seems likely that this new compound, m.p. 149-52°C is 3-cyclohexene-carboxamide, however, a more thorough characterization is necessary before this assign-

TABLE III

Birch Reduction of Benzamide

	Metal	Equivalent of Metal	Ethanol 95%	Benzamide	Experimental Conditions	Temperature of the bath	Products (crude)
I	3.0 g (0.42 mole) Lithium	3.39	150 ml	15.0 g (0.124 mole)	Niem's Procedure (27). Add first lithium, than add ethanol and neutralize with 10% Hcl after evap'n. of NH_3	Dry-ice (-78°C)	No isolatable product obtained
II	3.0 g (0.42 mole) Lithium	3.39	150 ml	15.0 g (0.142 mole)	Same as above I. Neutralization of the residue with 10% Hcl was omitted	Dry-ice	1,4-dihydro-benzamide (9.5 g; 63.3%)
III	6.44 g (0.28 mole) Sodium	3.42	135 ml	10.0 g (0.081 mole)	Kuehne & Lambert's Procedure (20). Add ethanol first, than add sodium	Dry-ice	1,4-dihydro-benzamide (6. g; 66%)
IV	9.2 g (0.40 mole) Sodium	5.0	240 ml	10.0 g (0.081 mole)	Kuehne & Lambert's Procedure (20) Same as above III	Dry-ice	1,4-dihydro-benzamide (6.0 g; 60%)
V	6.44 g (0.28 mole Sodium	3.42	135 ml	10.0 g (0.081 mole)	Kuehne & Lambert's Procedure (20) Same as above III & IV	Boiling point of NH_3 -33°C	Some reduced product, not fully identified. 6.8 g, 68%, m.p. 149-52°C

ment can be made. A further study of the effect of temperature on Birch reduction would be very desirable.

In case of m-methoxybenzamide, it has been reported (20) that m-methoxybenzamide is recovered unchanged when subjected to Birch reduction with 3.3 equivalents of sodium in ammonia and ethanol. Since the introduction of a substituent into the aromatic ring which would help to stabilize the amide anion, could make the amide sufficiently acidic to render it susceptible to reduction (20), i.e., m-methoxybenzamide (with $\sigma_{m\text{-}OCH_3} = +0.12$) is more acidic than benzamide. Methoxyl group ordinarily is strong electron donating but when present in m-position (with positive σ-value) apparently acts as a weak electron attracting. The degree of stabilization by the methoxyl substituent is also seen from a comparison of the acidities of benzoic acid and m-methoxybenzoic acid, Table I. So the possibility of undergoing Birch reduction with 3.3 equivalents of sodium and ethanol in liquid ammonia is more pronounced for m-methoxybenzamide than for benzamide. Experimental results of the present investigation (1st, 2nd, and third reduction, Table IV) contradicts the above reported failure (20) of ring reduction with 3.3 equivalents of sodium-ethanol and liquid ammonia. The experimental conditions were exactly similar to that of Kuehne and Lambert's (20) except possibly that of temperature, since they did not specify the

TABLE IV

Birch Reduction of m-Methoxybenzamide

	Sodium	Equivalent of Sodium	Ethanol 100%	m-Methoxy-benzamide	Experimental Conditions	Temperature of the bath	Products
I	5.3 g or (0.231 mole)	3.5	135 ml	10.0 g or (0.066 mole)	Kuehne & Lambert's Procedure (20). First add ethanol, and then add sodium	Dry-ice (-78°C)	1,4-Dihydro-3-methoxybenzamide (9.7 g, 97%*)
II	5.3 g (0.231 mole)	3.5	135 ml	10.0 g (0.066 mole)	Same as above I. 1 ml. (or 1 p.p.m.) of $FeCl_3$ in tetrahydrofuran added in the beginning.	Dry-ice	1,4-Dihydro-3-methoxybenzamide (7.18 g, 71.8%*)
III	1.59 g (0.069 mole)	3.3	25 ml	3.2 g (0.021 mole)	Kuehne & Lambert's Procedure (20), Same as I above.	Dry-ice	1,4-Dihydro-3-methoxybenzamide (2.6 g, 81%*)
IV	12.14 g (0.528 mole)	8.0	135 ml	10.0 g (0.066 mole)	Kuehne & Lambert's Procedure (20), Same as I above.	Dry-ice	Brownish liquid, (6.0 g) unidentified
V	2.65 g (0.115 mole)	3.5	67.5 ml	5.0 g (0.033 mole)	Kuehne & Lambert's Procedure (20), Same as I above.	Boiling point of ammonia (-33°C)	Yellowish white solid m.p. 138-43°C (4.0 g, 80%) unidentified

*This percentage yield is based on crude product.

temperature they used. All these reductions I, II, and III, Table IV were conducted at dry-ice temperature (-78°C).

The next reduction V, Table IV, was carried out at -33°C, the boiling point of ammonia, and according to Kuehne and Lambert's procedure (20), whereby a light yellowish white product, m.p. 139-43°C was obtained. This product showed strong absorption at 290 mu and 254 mu, and its infrared spectrum does not resemble with that of either m-methoxybenzamide or 1,4-dihydro-3-methoxybenzamide. Since it absorbs at 290 mu and 254 mu, so it may be some tetrahydro-derivative with a conjugate double bond, Figure 42. Much more work is required to characterize this compound.

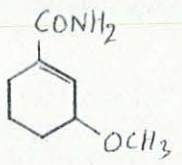


Figure 42

It was also found that addition of 0.001 mg of iron per ml. of the reaction mixture (added as ferric chloride dissolved in tetrahydrofuran), in reduction II, Table IV, does not have any dramatic effect on Birch reduction of m-methoxy-benzamide. It does perhaps lower the yield by about 10-15%.

It has also been reported (20) that m-methoxybenzamide was reduced to 1,4-dihydro-3-methoxybenzamide when eight equivalents of sodium and ethanol in liquid ammonia was used. Thus excess of sodium was used to satisfy the

competing reaction with ethanol. In the present investigation, when eight equivalents of sodium was used in the Birch reduction of m-methoxybenzamide, fourth reduction, Table IV, a light brownish liquid was obtained in contradiction to the above report (20). Of course, present reduction was carried out at dry-ice (-78°C) temperature. This liquid absorbs strongly at 300 mu and 250 mu. However, this compound was not identified.

Contrary to the previous reports (20,29,36), it was found in the present investigation that benzamide undergoes Birch reduction quite smoothly by both the methods (20,25, 27) at dry-ice (-78°C) temperature yielding approximately 60-65% of crude 1,4-dihydrobenzamide. Similarly m-methoxybenzamide on Birch reduction with 3.3 equivalents of sodium, ethanol and liquid ammonia at dry-ice temperature yields 1,4-dihydro-3-methoxybenzamide in fairly high yields (approximately 80-96%).

Reduction of terephthalic with lithium and ethanol in liquid ammonia at dry-ice temperature (-78°C) gave a mixture of cis- and trans- 1,4-dihydro-terephthalic acid in about 80-85% yield. It has been reported (20) that reduction products of terephthalic acid were not characterized quantitatively, because of their high decomposition point. The chemical reduction of terephthalic acid with sodium amalgam in freezing mixture, has been reported (23)

to give a mixture of cis- and trans-1,4-dihydroterephthalic acid, Figure 43 and 44 respectively.

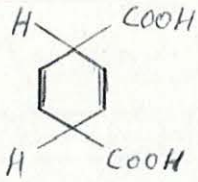


Figure 43

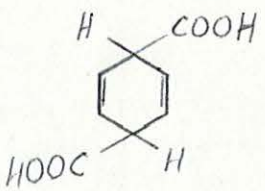


Figure 44

The cis- and trans- isomers were separated on the basis of difference of solubility in cold water, as cis-isomer is much more soluble in cold water than trans-isomer. Further purification of trans-acid was done by recrystallization from ethyl acetate. A dimethyl ester of trans-acid with methanol, phosphorus pentachloride and phosphorus oxychloride was made, though the product was not very pure. The cis-acid failed to give any dimethyl ester by this method. It would be very desirable to explore a suitable method for esterification of both trans- and cis-isomers.

SUMMARY

1. In a variety of experimental procedures for Birch reduction at dry-ice temperature (-65 to -78°C), benzamide was reduced to 1,4-dihydrobenzamide:

a. By using Niem's procedure (27), with lithium and ethanol in liquid ammonia at dry-ice temperature and where ethanol was added slowly after lithium addition, benzamide was reduced to 1,4-dihydrobenzamide.

b. By using Kuehne and Lambert's method (20), with sodium and ethanol in liquid ammonia at dry-ice temperature, benzamide was reduced to 1,4-dihydrobenzamide.

c. Using Kuehne and Lambert's procedure (20), with sodium and ethanol in liquid ammonia at -33°C (the boiling point of NH_3), benzamide was reduced to a new compound (possibly 3-cyclohexene-carboxamide) not fully characterized.

2. m-Methoxybenzamide when subjected to Birch reduction at -78°C or -33°C and with a 3.3 or 8 equivalents of sodium and ethanol by Kuehne and Lambert's procedure (20), gave the following results:

a. With 3.3 equivalents of sodium and ethanol in liquid ammonia at -78°C, m-methoxybenzamide was reduced to 1,4-dihydro-3-methoxybenzamide.

b. A reduction similar to (a) with added iron

(1 p.p.m.), was done with no noticeably large effects.

c. Birch reduction of m-methoxybenzamide at -33°C (the boiling point of ammonia), gave a new compound, not identified.

d. m-Methoxybenzamide, with excess of sodium (8 equivalents) at dry-ice temperature, was reduced to a light brownish liquid, not characterized.

3. Terephthalic acid on Birch reduction with lithium and ethanol in liquid ammonia was reduced to a mixture of cis- and trans- 1,4-dihydroterephthalic acid. Cis- and trans-isomers were separated on the basis of difference in solubility, as cis-isomer is more soluble in cold water than trans-isomer.

EXPERIMENTAL

The following are some of the general procedures used in this investigation:

a. In all the reductions the ammonia was collected by condensing ammonia vapors (coming from the gas tank) using a dry-ice acetone condenser and a cooling bath. The ammonia undoubtedly contained small amounts of water.

b. Unless otherwise stated, each reduction was done in a 2-liter three necked round bottom flask equipped with a mechanical stirrer with a Teflon blade, a dry-ice condenser, and a dropping funnel.

c. A rotatory evaporator, with vacuum from a water aspirator was used for evaporation and concentration purposes.

d. Melting points of all the compounds were determined on Thomas Hoover, capillary melting point apparatus unless otherwise specified.

e. A Beckman D.B. Spectrophotometer (U.S.A. made) was used for ultra-violet spectra.

f. A Perkin-Elmer, Model 137 B, Infracord Spectrophotometer was used for infrared spectra.

A. REDUCTION OF BENZAMIDE

First Reduction of Benzamide (Lithium metal, Niem's procedure, (27).

Fifteen grams (0.124 mole) of benzamide (Eastman Organic Chemicals, m.p. 130-32°) was added to 800 ml of liquid ammonia. The solution was stirred at dry-ice temperature while 3 g. (0.42 mole) of lithium was added in small pieces over 20 minutes. Then 150 ml. of 95% ethanol was added over 30 minutes. After disappearance of the blue color (1-2 minutes), 30 g. (0.56 mole) of ammonium chloride was added. The ammonia was allowed to evaporate when the reaction mixture was allowed to stand overnight. The residual material was dissolved in 150 ml. of ice-cold water. After acidification with 10% hydrochloric acid, the solution was extracted with four 100 ml. portions of ether. The combined ether solution was dried over an anhydrous magnesium sulfate. Evaporation of the ether under vacuum left a thick brownish liquid. An attempt to crystallize 1,4-dihydrobenzamide from this liquid by dissolving it in hot benzene and cooling was unsuccessful.

Second Reduction of Benzamide (Lithium metal, Niem's procedure (27).

Same quantities of reagents were used here as in the

first reduction and in the same order. This time acidification with 10% hydrochloric acid was omitted, as its use is apparently not necessary and moreover it had appeared to cause the decomposition of the reduced product in the first reduction. In this case, the ether solution after being dried over an anhydrous magnesium sulfate and after being evaporated to dryness under vacuum gave 9.5 g. (63.3%) of residue, m.p. 140-47°C. After four recrystallization from benzene, 3.9 g. of 1,4-dihydro-benzamide m.p. 154-55°C was obtained, which showed only end absorption in the ultraviolet region. The infrared spectrum also indicated lack of absorption in aromatic double bond region and resembled the I.R. of 1,4-dihydrobenzamide reported by Tony Niem (27). Its N.M.R. spectrum also was similar with the N.M.R. spectrum of 1,4-dihydrobenzamide prepared by Niem (27).

Third Reduction of Benzamide (Sodium metal, Kuehne & Lambert's procedure (20).

Ten grams (0.082 mole) of benzamide (m.p. 130-32°C) in 135 ml of 95% ethanol was added to 800 ml of liquid ammonia in a 2-liter three necked flask. The solution was stirred vigorously at dry-ice temperature, while 6.44 g. (0.28 mole) of sodium was added in small pieces over 10 minutes. After the disappearance of the blue color (1-2 minutes), 20 g. (0.373 mole) of ammonium chloride was

added and then the ammonia was allowed to evaporate when the reaction mixture was allowed to stand overnight. The reaction mixture was evaporated to dryness in vacuo at room temperature and 230 ml. of distilled water was added. The slurry was extracted 7-8 times with 75 ml. portions of methylene chloride. After being washed with water and once with saturated salt solution, the methylene chloride solution was dried over an anhydrous magnesium sulfate. The dried extracts were concentrated in vacuo to dryness and 6.6 g. (66%) of crude solid product remained, m.p. 141-47°C. After 4-5 recrystallizations from benzene, 3.2 g. of material m.p. 154-55°C was obtained. Its U.V. and I.R. spectrums were similar with that of the 1,4-dihydrobenzamide previously prepared.

Fourth Reduction of Benzamide (Sodium metal, Kuehne & Lambert's General Procedure (20).

A solution of 10 g. (0.082 mole) of benzamide in 240 ml of 95% ethanol was added to 1360 ml of liquid ammonia. The solution was stirred rapidly at dry-ice temperature and 9.2 g. (0.41 mole) of sodium was added over 5-10 minutes. When the reaction was complete, as seen by a disappearance of blue color, 42 g. (0.83 mole) of ammonium chloride was added. The ammonia was allowed to evaporate by standing overnight at room temperature. Five hundred ml of distilled water

was then added and the reaction mixture extracted thoroughly with methylene chloride. The extracts were washed with water and once with saturated sodium chloride solution, dried over an anhydrous magnesium sulfate and concentrated in vacuo leaving 6.0 g. of crude product, m.p. 148-52°C. The product was recrystallized two times from benzene yielding 2.0 g. of material with m.p. 154-55°C. This material showed no U. V. absorption and its I. R. spectrum is similar to that of 1,4-dihydrobenzamide previously prepared.

Fifth Reduction of Benzamide (Sodium metal, Kuehne & Lambert's procedure (20) at -33°C).

(Formation of unidentified reduction product)

The procedure for this particular experiment was exactly the same as the third reduction, using the same quantities except that the reduction was carried out at -33°C, the boiling point of ammonia instead of dry-ice temperature (-65 to -78°C). The methylene chloride solution on evaporation to dryness in vacuo gave, 6.8 g. (68%) of crude product, m.p. 89-110°. This after 3 recrystallization from benzene gave 1.3 g. of reduced product m.p. 149-52°C. It showed only end absorption and its I.R spectrum was different than that of either pure 1,4-dihydrobenzamide or benzamide alone. From the comparison of the melting points

of related reduced products, it may be that this compound is 3-cyclohexene-carboxamide (literature m.p. 152°). However, more work would be necessary before any structure assignment could be made.

B. REDUCTION OF m-METHOXYBENZAMIDE

First Reduction of m-methoxybenzamide (20).

A solution of 10 g. (0.066 mole) of m-methoxybenzamide (K & K Laboratories, Inc.; m.p. 134-36°C) in 135 ml of 100% ethanol was stirred vigorously with 800 ml of liquid ammonia. Five and three tenth grams (0.231 mole) of sodium was added in small pieces over a period of 5 minutes. After disappearance of the blue color, 20.0 g. (0.373 mole) of ammonium chloride was added and after an additional half an hour the ammonia was allowed to evaporate, when the reaction mixture was allowed to stand overnight. The residue was then dissolved in 230 ml. of distilled water and the slurry was extracted 7 times with 75-100 ml portions of methylene chloride. After being washed with water, once with saturated sodium chloride solution and dried over an anhydrous magnesium sulfate (Baker Analysed Reagent). The combined extracts were concentrated and ultimately evaporated to dryness in vacuo and yielded 9.7 g. (97%) of crude product, m.p. 135-44°C. Two recrystallizations from benzene-

petroleum ether gave 3.25 g. of dihydro-product, m.p. 161-63°C. This material's ultra-violet spectrum showed only end absorption. Infrared spectrum also showed lack of absorption in the aromatic double bond region (1480-1500u).

Second Reduction: Effect of iron on Reduction of m-methoxybenzamide

Eight hundred ml. of ammonia was condensed in a 2-liter three necked flask equipped with usual accessories. One ml. (1 p.p.m.) of iron chloride (0.1 g $FeCl_3$ H_2O dissolved in 100 ml. of tetrahydrofuran) was added into the liquid ammonia and stirred rapidly at dry-ice temperature. The rest of the procedure was exactly the same as in the first reduction of m-methoxybenzamide. A 7.18 g. (71.8%) of crude product, m.p. 135-58°C, was obtained. After four recrystallization, 2.8 g. of dihydro-3-methoxybenzamide was obtained, m.p. 145-58°C. It showed slight absorption at 280 mu and its I.R. spectrum was exactly similar to that of 1,4-dihydro-3-methoxybenzamide prepared in the first reduction.

Third Reduction of m-methoxybenzamide by Kuehne & Lambert's method (20)

The procedure was same as that of first reduction above, using 3.2 g. (0.021 mole) of m-methoxybenzamide, 25 ml of 100% ethanol, 320 ml. of liquid ammonia, 1.59 g.

(0.069 mole) of sodium and 15.0 g. (0.28 mole) of ammonium chloride. A 2.6 g. (81%) of crude product was collected, m.p. 110-130°C, which after 3 recrystallization from benzene-petroleum ether gave 0.75 g. of reduced 1,4-dihydro-product, m.p. 158-62° C.

Fourth Reduction of m-methoxybenzamide with excess (8 equivalents of Sodium (20), by Kuehne and Lambert's procedure

Ten grams (0.066 mole) of m-methoxybenzamide in 135 ml. of 100% ethanol was added to 800 ml. of liquid ammonia. With vigorous stirring at dry-ice temperature, 12.14 g. (0.528 mole, 8 equivalents) of sodium was added over 5-10 minutes. After completion of the reaction (4-8 minutes), 46.9 g. (0.876 mole) of ammonium chloride was added. The isolation procedure was as in the previous reduction procedures. Six grams of brownish liquid with a little solid material was obtained. Its ultra-violet spectrum showed absorption at 300 mu and 250 mu and is different than that either m-methoxybenzamide or 1,4-dihydro-derivative. Also its infrared spectrum differs from that of 1,4-dihydro-3-methoxybenzamide or m-methoxybenzamide.

Fifth Reduction of m-methoxybenzamide at -33°C

The procedure for this experiment was the same as the first reduction of m-methoxybenzamide except that exactly

half of all the quantities were used. Also this experiment was carried out at -33°C, the boiling point of ammonia instead of dry-ice temperature. A 4.0 g. of crude product was obtained, m.p. 135-45°C. After 3 recrystallization from benzene-petroleum ether, 1.4 g. of yellowish white solid product, m.p. 138-43°C was obtained. It showed strong absorption at 290 mu and 254 mu, resembling somewhat with m-methoxybenzamide or 1,4-dihydro-3-methoxybenzamide or the above compound prepared in the fourth reduction.

C. REDUCTION OF TEREPHTHALIC ACID

Preparation of Terephthalic acid by hydrolysis of Terephthalic acid dimethyl ester

Thirty grams of terephthalic acid dimethyl ester (Eastman Org. Chemicals) was dissolved in sodium hydroxide solution (90 g/300 ml. H_2O), and allowed to stand for about 36 hours. The solution was filtered and neutralized with 6-M hydrochloric acid to the pH to 2. The free terephthalic acid was collected by filtration, washed with water and was dried in a vacuum desicator. It sublimed without melting at 300°C. It showed ultra-violet absorption at 285 mu, 240 mu and 223 mu.

First Reduction of Terephthalic acid

Ten grams (0.06 mole) of terephthalic acid, dissolved in 100 ml. of 95% ethanol, was added to 600 ml. of liquid ammonia in a 2-liter three necked flask. Then 2 g. (0.27 mole) of lithium in small pieces was added to the well stirred solution at dry-ice temperature. After all the lithium has been consumed, as evidenced by the disappearance of the blue color, 14.6 g. (0.37 mole) of ammonium chloride was added cautiously. The mixture was stirred for an additional hour and then allowed to stand overnight until the ammonia had evaporated.

The residue was dissolved in 300 ml. of water and the solution was poured onto 200 g. of ice and acidified to a pH of about 4 by addition of 75 ml. of 10% hydrochloric acid. The resulting mixture was extracted with four 100 ml. portions of peroxide-free ether. The combined ether extracts were washed with 50 ml. of saturated salt solution and dried over 2 g. of anhydrous magnesium sulfate. The dried ether extract was concentrated at 25-50°C under reduced pressure. Eight and five tenth gram of crude product was collected. It charred at 270°C.

Separation of Cis- and Trans- 1,4-dihydroterephthalic acid (23).

Five grams of the above mixture was dissolved in 100 ml. of distilled water. The solution was boiled for five minutes. After the solution cooled, the white residue (A) was collected by filtration. The filtrate was extracted with four 50 ml. potions of ether. The combined ether extracts were dried over an anhydrous magnesium sulfate for 2-3 hours, and evaporated under vacuum and a white residue remained. This white residue (2 g.) was dissolved in 10 parts of hot water and the solution was cooled quickly in ice-cold water. The solution was filtered and the filtrate was saturated with sodium chloride and cis- 1,4-dihydro-terephthalic acid precipitated. It was collected by filtration and the filtrate was again saturated with sodium chloride and the precipitate which appeared in the solution was also collected by filtration. The precipitate was washed with a little cold water. The filtrate was extracted with two 20 ml. portions of ether to recover the remaining cis- 1,4-dihydroterephthalic acid if any. The ether extract upon evaporation gave a small amount of the cis- acid. The combined samples of cis- acid weighed about 1 g., decomposed at 270°C. It also absorbs at 270 mu and 240 mu.

The above white residue (A) (2.8 g.) which is

mostly trans- 1,4-dihydroterephthalic acid was recrystallized from ethyl acetate. It does not melt at 270°C. It showed strong absorption at 270 and 240 mu.

Derivatives:

a. Dimethyl ester of Trans- 1,4-dihydroterephthalic acid (23)

In a 100 ml. round bottomed flask fitted with a reflux condenser was placed 0.48 gram of trans- acid and 20 ml. of anhydrous methanol was added with rapid stirring. Then 1 g. of phosphorus pentachloride and 2 drops of phosphorus oxychloride were added. After being stirred for a few minutes, the flask was immersed in warm water for about 45 minutes. Evaporation of the solvent under vacuum left a residue which was dissolved in petroleum ether (b.p. 30-60°C). The petroleum ether solution was concentrated at reduce pressure and the white crystals of trans- acid dimethyl ester were dried in vacuum desicator under reduced pressure. 0.36 g. of crude dimethyl ester was collected, m.p. 47-52°C (Literature, m.p. 77°C). Its U.V. spectrum showed absorption at 270 mu and 240 mu.

b. Cis- 1,4-dihydroterephthalic acid dimethyl ester

The procedure was exactly similar to that of trans- acid dimethyl ester described above, using 0.2 g. of cis-

acid. After completion of the reaction, cis- acid was recovered unreacted.

Second Reduction of Terephthalic acid.

The procedure was the same as for the first reduction with the exception of the following changes:

i. The combined ether extracts are washed with 75 ml. saturated salt solution. The ether extract containing a suspension of white material was filtered and the filtrate was dried over anhydrous magnesium sulfate. Residue on the filter about 2.1 g. was found to be unreacted terephthalic acid. It decomposes at 300°C.

ii. The dried ether extract (i) was evaporated to dryness and 6.8 g. of crude product (mixture of cis- and trans- acid) was collected. It decomposes at 270°C and showed absorption at 270 mu and 240 mu.

The procedure for separation of cis- and trans- 1,4-dihydroterephthalic acid was as for the first reduction.

Purification of Trans- 1,4-dihydroterephthalic acid

It was purified by recrystallization from ethyl acetate. After 3 recrystallizations the product was considerably much purer as was shown by U.V. absorption. But still it showed some absorption at 270 and 240 mu.

Purification by recrystallization from ether was also tried but without any success.

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